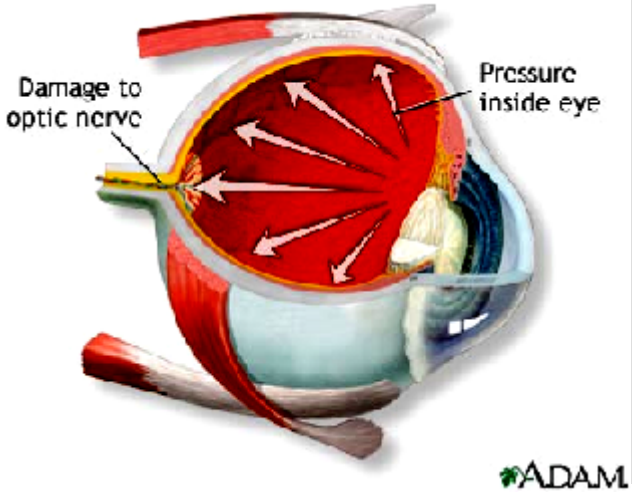
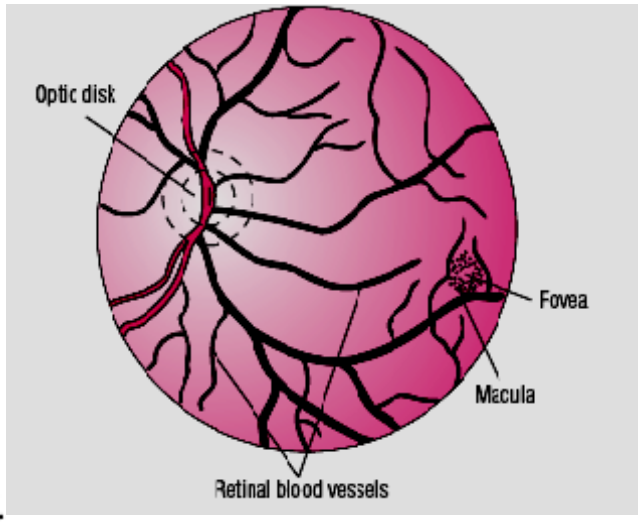
Glaucoma

Definition :

Glaucoma, in ancient Greek, meant" clouded " [1].

Glaucomas are ocular disorders characterized by structural changes in the optic nerve head (optic disk) and by functional changes in the visual field [1,2]. The optic disc (the point at which the nerve fibres from the retina merge to form the optic nerve) [1].





Pathophysiology [2]:

The key to understanding the pathophysiology and treatment of POAG relies on an understanding of aqueous humor dynamics [3].

- The ciliary body, produces and secretes fluid called aqueous humor into the posterior chamber.
- After the transport of aqueous humor into the posterior chamber, it flows through the pupil into the anterior chamber where it provides oxygen and nutrition to the lens and cornea .
- Aqueous humor then exits the anterior chamber through the trabecular meshwork and drains into Schlemm's canal which drains aqueous humor into the venous system [3].
- ***IOP is determined by the balance between the inflow and outflow of aqueous humor.***
- ***Inflow is increased by β-adrenergic agents*** and decreased byα-2, α-, and β-adrenergic blockers; and carbonic anhydrase inhibitors [2].
- ***Outflow is increased by cholinergic agents***, and by ***prostaglandin analogs*** andα -2 ***adrenergic agonists*** [2].

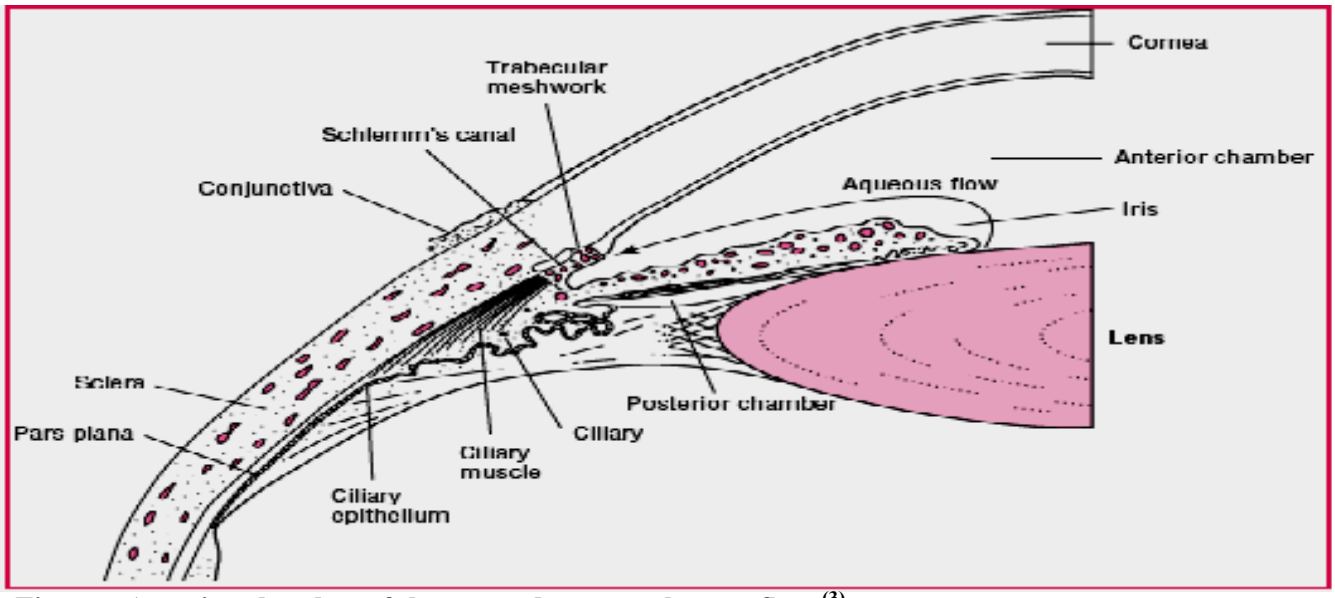


Figure : Anterior chamber of the eye and aqueous humor flow [3] .

In open-angle glaucoma, the specific cause of optic neuropathy is unknown. Increased intraocular pressure (IOP) was historically considered to be the sole cause [2].
Although IOP is a poor predictor of which patients will have visual field loss, the risk of visual field loss increases with increasing IOP [2].
closed-angle glaucoma, occurs when the iris mechanically block the trabecular meshwork resulting in increased IOP [2].

Types of glaucoma [1]

There are various types of glaucoma. Broadly the disease can be classified into four groups:
1-**Primary open angle glaucoma** This is the most common type of glaucoma in people over the age of 50. The anterior chamber is deep and there is ***reduced aqueous outflow*** through the trabecular meshwork, which in turn causes the ***lOP to increase.***
2-**Normal-tension glaucoma** In this type of glaucoma, the lOP is within the statistical normal. However, there may be ***poor blood flow to the optical disc*** or increased susceptibility to disc damage at lower lOP.
3-**Primary angle closure glaucoma** The lOP increase is caused by ***closure of the anterior*** chamber angle. This may be of acute or chronic type.
4-**Secondary open angle or angle closure glaucoma** These types of glaucoma result from other ocular conditions or treatments

Risk factors[1] :

Those with a strong association include:
1-**lOP** High lOP is the most important risk factor for developing glaucoma. The risk of glaucomatous damage increases with increasing lOP (especially above 22mmHg).
2-**Age** Incidence of POAG is higher in elderly than younger patients.
3-**Corneal thickness** : Patients with thinner corneas are lmore likely to progress to POAG.
4-**Family history** :A positive family history increases the relative risk of POAG.
Factors with a moderate association include:

1-**Myopia** 2-**Sex (**female more than female)

Factors with a weak association include:

1-**Diabetes** 2- **Migraine** 3- **Systemic hypertension**.

Clinical Presentation [2] :

Open-angle glaucoma is slowly progressive and is usually ***asymptomatic*** until the onset of substantial visual field loss**.**

In closed-angle glaucoma, patients typically experience ***intermittent prodromal symptoms*** (e.g., blurred or hazy vision with halos around lights and, occasionally, headache).

Acute episodes produce symptoms associated with a cloudy, edematous /cornea; ocular pain; nausea, vomiting, and abdominal pain; and diaphoresis.

Diagnosis [2]

The diagnosis of open-angle glaucoma is confirmed by the presence of characteristic optic disk changes
visual field loss,
with or without increased IOP.

Normal tension glaucoma refers to
disk changes,
visual field loss,
and IOP of less than 21 mm Hg.

Ocular hypertension refers to
IOP of more than 21 mm Hg
without disk changes or visual field loss.

Desired Outcome

The goal of drug therapy in patients with glaucoma is to ***preserve visual function*** by *reducing the IOP to a level at which no further optic nerve damage occurs* [2].

Treatment

Treatment is indicated for all patients with elevated IOP and characteristic optic disk changes or visual field defects [2].

1-Beta-Adrenergic Antagonists

- Topical β-adrenergic antagonists (β-blockers) are generally considered ***first-line*** agents for the treatment of POAG unless contraindications are present [3].
- Topical β-blockers decrease IOP ***by reducing the formation of aqueous humor***.
- **Timolol, levobunolol, metipranolol, and carteolol** are non-selective for β1- and β2-adrenergic receptors, while **betaxolol** has β1-selective properties. All of the topical β-blockers have similar efficacy and adverse-effect profiles [3].

- Topical β-blockers are typically ***administered twice daily***. A gel-forming solution of timolol (Timoptic-XE ®) can be administered once daily. Tachyphylaxis may occur in 20% to 50% of
- patients on monotherapy with a β-blocker, resulting in the ***need for a different agent*** or combination therapy [3].
- β-Blockers can cause significant ***systemic adverse effects*** , Bronchospasm is the most common pulmonary effect of topical β-blockers. Cardiovascular effects include bradycardia, hypotension, and congestive heart failure exacerbation.
- Topical β-blockers are generally ***contraindicated*** in patients with asthma, COPD , sinus bradycardia, 2nd - or 3rd -degree heart block, cardiac failure, and hypersensitivity to the product.
- ***Local side effects*** are usually ***tolerable*** and may be caused by preservatives, therefore switching from one product to another may alleviate the local side effects. ***Stinging of the eyes upon instillation*** is the most common adverse effect [3].
- Patients prescribed topical β-blockers ***should be counseled on the nasolacrimal occlusion technique*** (see evaluation of therapeutic outcome) to decrease systemic absorption[3]

2-Prostaglandin analogs

- The prostaglandin analogs,(including **latanoprost, travoprost, and bimatoprost**) reduce IOP by ***increasing the outflow of aqueous humor*** [3].
- ***They lower IOP more than β-blockers*** and unlike topical β-blockers, can effectively lower nocturnal IOP, providing IOP control throughout the day and night
- ***Interestingly***, administration of prostaglandin analogs twice daily may reduce the IOP comparably to once-daily dosing [2] ***(twice daily may decrease effectiveness***)
- The drugs are ***administered at nighttime***, although they are probably as effective if given in the morning [2].
- Prostaglandin analogs are well tolerated and produce ***fewer systemic adverse effects*** than timolol. ***Local ocular*** tolerance generally is good :

A-**Conjunctival hyperaemia** (the appearance of red eye) [4] .
B-**Iridial pigmentation** (alteration of the colour of the irises resulting in a darker more intense eye colour) [4] .
C-**Hypertrichosis** (eyelashes grow in all dimensions and darken). The hypertrichotic effect appears to be similar for all three agents [4] .

3-Alpha2-Adrenergic Agonists

- **Brimonidine** and **Apraclonidine** are α2-adrenergic agonists that decrease IOP by reducing aqueous humor production.
- Brimonidine has a ***higher selectivity to the α2 receptor*** than apraclonidine [3] .
- **Apraclonidine** is often used for the ***prevention and treatment of post-surgical IOP elevations*** and ***no longer commonly*** used for long-term treatment of POAG [3] because of a high incidence of loss of control of IOP (tachyphylaxis) and a more severe and prevalent ocular allergy rate [2] .
- **Brimonidine** is considered a first-line or adjunctive agent in t

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- Patients prescribed brimonidine should be counseled on ***the nasolacrimal occlusion technique (NLO)*** to reduce systemic adverse effects and to improve efficacy [3].
- Brimonidine is usually administered every 8 hours. A 12-hour dosing schedule may be employed by using nasolacrimal occlusion when instilling the drops[3] .

4-Carbonic anhydrase inhibitors (CAIs)

A-Topical agents

- **Dorzolamide and brinzolamide** are the only topical CAIs available and lower IOP by 15% to 24%.
- Both medications are administered every 8 hours and are used as adjunctive therapy or as monotherapy for patients that cannot tolerate first-line agents [3].
- Nasolacrimal occlusion may allow for dosing every 12 hours [3].
- ***Systemic adverse effects*** are unusual [2]. ***Local side effects*** include burning, stinging, itching, foreign body sensation, dry eyes, and conjunctivitis.
- Brinzolamide may have a lower incidence of these side effects since the drug is in a neutral pH solution [3].
- Both topical CAIs are sulfonamides and are contraindicated in patients with history of ***sulfonamide hypersensitivity*** [3](all CAIs, topical or systemic, contain sulfonamide moieties) [2].
- The combination product timolol 0.5% and dorzolamide 2% (Cosopt) is dosed twice daily and produces equivalent IOP lowering to each product dosed separately [2].

B-Systemic CAIs

- There are three systemic CAIs : **acetazolamide, dichlorphenamide, and methazolamide**.
- These agents effectively lower IOP by 20% to 30% but are reserved ***as third-line*** agents [3]. (in patients failing to respond to or tolerate maximum topical therapy [2]) because of their significant adverse effects [3].
- The systemic CAIs can also be ***used to lower IOP in acute angle-closure*** glaucoma[3].
- Acetazolamide has an ***intravenous formulation t***hat can be utilized in patients having ***nausea due to the angle-closure*** attack[3].
- They are also contraindicated [3] (or used with caution [2]) in patients with Sulfonamide allergy.
- Acetazolamide and methazolamide are considered the best-tolerated CAIs [2].
- ***Systemic and topical CAIs should not be used in combination*** because no data exist concerning improved IOP reduction, and the risk for systemic adverse effects is increased [2].

5-Parasympathomimetic drugs

- Parasympathomimetic drugs mimic the effects of stimulating the parasympathetic nervous system.
- In the eye, this results in an ***increased outflow of aqueous humour*** . The main parasympathomimetic used to lower lOP is **pilocarpine** [3].

- Stimulating the parasympathetic nervous system in the eye also ***causes pupil constriction, which reduces the amount of light entering the eye and also the overall field of vision.***
- This can be a particular problem for glaucoma patients, who often have a significant loss of visual field. This, together with the fact that it needs to be administered three ***to four times daily***, contributes to poor patient compliance [3].

6-Non-selective Adrenergic Agonists

- **Epinephrine and its prodrug, dipivefrine**, are rarely used for the treatment of glaucoma and are considered ***last-line agents*** because of their systemic side-effect profile.
- **Dipivefrine** enhances the ***corneal penetration..***
- ***Systemic side effects*** include palpitations, increased blood pressure, and arrhythmia, and therefore they should be used with caution in patients with cardiovascular disease, cerebrovascular disease, and hyperthyroidism.
- Using the nasolacrimal occlusion technique may decrease systemic effects [3].

Nonpharmacologic Therapy

- When drug therapy fails, is not tolerated, or is excessively complicated, surgical procedures such as ***laser trabeculoplasty or a surgical trabeculectomy*** may be performed to improve outflow [2].
- Laser trabeculoplasty uses laser energy aimed at the trabecular meshwork to improve the outflow. approximately 50% of laser trabeculoplasty procedures will fail at 10 years.
- Trabeculectomy is the removal of a portion of the trabecular meshwork to improve aqueous humor outflow. Failure rates of trabeculectomy are less compared to laser trabeculoplasty (20% to 30% failure at 10 years) [3].

Treatment of Closed –Angle Glaucoma [2]

- Acute closed-angle glaucoma with high IOP requires ***rapid reduction of IOP.***
- ***Iridectomy*** is the definitive treatment, which produces ***a hole in the iris*** that permits aqueous flow to move directly from the posterior to the anterior chamber.
- Drug therapy of an ***acute attack typically*** consists of an **osmotic agent and secretory inhibitor (e.g., β blocker, α2 agonist, latanoprost, or CAI), with or without pilocarpine.**
- Osmotic agents are used because they rapidly decrease IOP. Examples include **glycerin,** 1 to 2 g/kg orally, and **mannitol,** 1 to 2 g/kg intravenously.
- Although traditionally the drug of choice, ***pilocarpine use is controversial as initial therapy.***
- Once IOP is controlled, pilocarpine ***should be given every 6 hours until iridectomy*** is performed.
- **Topical corticosteroids** can be used to reduce ocular inflammation .

Evaluation of Therapeutic Outcomes [2]

1-Monitoring therapy for open-angle glaucoma should be individualized. IOP response is assessed every 4 to 6 weeks initially, every 3 to 4 months after IOP become acceptable, and more frequently after therapy is changed. The visual field and disk changes are monitored annually, unless glaucoma is unstable or worsening.
2-There is no specific target IOP because the correlation between IOP and optic nerve damage is poor. The target IOP also depends on disease severity and is generally less than 21 mm Hg for early visual field loss or optic disk changes, with lower targets for greater damage. Targets as low as less than 10 mm Hg are desired for very advanced disease, and normal tension glaucoma .
3-Using more than one drop per dose increases the risk of adverse events and cost, but not efficacy.
4-Patients should be educated about possible adverse effects and methods for preventing them.
5-Patients should be taught how to administer topical therapy. To maximize topical activity and minimize systemic absorption, the patient should close the lid for 1 to 3 minutes after instillation and place the index finger over the nasolacrimal drainage system in the inner corner of the eye.
6-If more than one topical drug is required, instillation should be separated by 5 to 10 minutes to provide optimal ocular contact.
7-Adherence to drug therapy should be monitored because it is commonly inadequate and a cause of therapy failure .

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للاطلاع فقط

TABLE 92–4. Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic blocking agents						
Betaxolol	Relative β_1-selective	Generic	Solution	0.5	1 drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	1 drop twice a day	
Carteolol	Nonselective, ISA	Generic	Solution	1	1 drop twice a day	
Levobunolol	Nonselective	Betagan	Solution	0.25, 0.5	1 drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	1 drop twice a day	
Timolol	Nonselective	Timoptic, Betimol	Solution	0.25, 0.5	1 drop every day—one to two times a day	
		Timoptic-XE	Gelling solution	0.25, 0.5	1 drop every day[a]	
Nonspecific adrenergic agonists						
Dipivefrin	Prodrug	Propine	Solution	0.1	1 drop twice a day	Increased aqueous humor outflow
α_2-Adrenergic agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	1 drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow
Brimonidine		Alphagan P	Solution	0.15	1 drop two to three times a day	
Cholinergic agonists						
Direct-acting						
Carbachol	Irreversible	Carboptic, Isopto Carbachol	Solution	0.75, 1.5, 2.25, 3	1 drop two to three times a day	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Irreversible	Isopto Carpine, Pilocar	Solution	0.25, 0.5, 1, 2, 4, 6, 8, 10	1 drop two to three times a day 1 drop four times a day	
		Pilopine HS	Gel	4	Every 24 h at bedtime	
Cholinesterase inhibitors						
Echothiophate		Phospholine Iodide	Solution	0.125	Once or twice a day	
Carbonic anhydrase inhibitors						
Topical						
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt	Solution	2	Two to three times a day	
Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
			Injection	500 mg/vial	250–500 mg	
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Dichlorphenamide		Daranide	Tablet	50 mg	25–50 mg one to three times a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25–50 mg two to three times a day	
Prostaglandin analogs						
Latanoprost	Prostaglandin $F_{2\alpha}$ analog	Xalatan	Solution	0.005	1 drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Bimatoprost	Prostamide analog	Lumigan	Solution	0.03	1 drop every night	
Travoprost		Travatan	Solution	0.004	1 drop every night	
Combinations						
Timolol-dorzolamide		Cosopt	Solution	Timolol 0.5% Dorzolamide 2%	1 drop twice daily	

[a]Use of nasolacrimal occlusion will increase number of patients successfully treated with longer dosage intervals.
ISA, intrinsic sympathomimetic activity.

Further reading (للإطلاع)

1-Prostaglandin Analogs

Local side effectsa of The prostaglandin analogs :

A-Conjunctival hyperaemia (the appearance of red eye) [4].

Conjunctival hyperemia or is a common adverse effect caused by a vasodilatory effect . It is most prominent early in therapy and usually subsides over time. While generally a benign adverse effect, patients may have a concern if it affects their cosmetic appearance. Latanoprost has the lowest incidence of hyperemia (14% to 27.6%) compared to bimatoprost (9% to 46%) and travoprost (49.5%) [3].

B-Iridial pigmentation (alteration of the colour of the irises resulting in a darker more intense eye colour) [4].

It occur most commonly in on long-term prostaglandin analog therapy (the irides become darker because of increased production of melanin) [3].

Latanoprost appears have the highest incidence of iris pigmentation compared to travoprost and bimatoprost . The increase in pigmentation may be irreversible or may reverse at a very slow rate. Increased iris igmentation appears to be only a cosmetic effect [3].

2-Alpha2-Adrenergic Agonists

Brimonidine lowers IOP by 14% to 28%.

An allergic-type reaction characterized by lid edema, eye discomfort, foreign-object sensation, itching, and hyperemia occurs in approximately 30% of patients with apraclonidine. Brimonidine produces this adverse effect in up to 8% of patients. This reaction commonly necessitates drug discontinuation. Systemic adverse effects with brimonidine include dizziness, fatigue, somnolence, dry mouth, and possibly a slight reduction in blood pressure and pulse [2].

Brimonidine-purite 0.1% and 0.15% solution (Alphagan P®) has similar efficacy compared to the brimondine 0.2% solution [3] because the more neutral pH of brimonidine-purite allows for higher concentrations of brimonidine in the aqueous humor [2].

3-The systemic CASs

The systemic CASs are associated with significant adverse effects which include paresthesias of the hands and feet, nausea, vomiting, and weight loss. Patients can develop systemic acidosis, hypokalemia, hyponatremia, and nephrolithiasis due to the inhibition of renal carbonic anhydrase [3].

Renal failure, hepatic insufficiency, chronic obstructive pulmonary disease, and decreased serum potassium and sodium levels are all contraindications of systemic carbonic anhydrase inhibitor therapy [3].

4-Pilocarpine

Systemic side effects of pilocarpine include hypersalivation, bronchoconstriction, nausea and vomiting, and diarrhoea. Patients with cardiovascular conduction system disease may be at risk of developing AV block if pilocarpine is used intensively.' Attempts have been made to limit systemic side effects and improve compliance with sustained release preparations of pilocarpine.' For example, Ocusert-Pilo is a slow release ophthalmic delivery system of pilocarpine encapsulated in a semi-permeable membranous reservoir. The device is placed under the eyelid and left in place for seven days, releasing a dose of pilocarpine at 20 or 40 micrograms per hour.' An alternative is a sustained release gel formulation of pilocarpine. This is applied at bedtime to provide 24h control of the lOP and has been shown to reduce the incidence of the adverse effect of myopia [4].